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IN THE CLAIMS:

Please cancel claims 189-204 without prejudice.

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REMARKS

Claims 189-204 have been withdrawn in view of the restriction requirement and, accordingly, are canceled herein without prejudice. Applicants expressly reserve the right to pursue canceled or unclaimed subject matter in one or more continuation, divisional or continuation-in-part applications. After entry of this amendment, claims 171-188 and 205-286 will be pending.

Applicants acknowledge that the Examiner has withdrawn the rejections under 35 U.S.C. § 102 (a) and (b). With regard to the comments, objections and rejections presented in the Action by the Examiner, Applicants' response continues below.

The Rejection Under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 171-188, and 205-286 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kim (WO 93/20229) and/or Cheresh (WO 89/05155) in view of Nicosia et al. (Am. J. Pathol., 138:829-833, 1991; "Nicosia"), Nip et al. (J. Clin. Invest., 90:1406-1413, 1992; "Nip"), Folkman et al., (Seminars in Cancer Biology, 3:89-96, 1992; "Folkman"), Pignatelli et al. (Hum. Pathol., 23:1159-1166, 1992; "Pignatelli") and art known procedures of treating cancers of interest at the time the invention was made.

The pending claims relate to administering a monoclonal antibody immunospecific for $\alpha_v\beta_3$ in methods of (i) inhibiting breast tumor tissue growth (claims 171-188); (ii) inhibiting metastatic solid tumor tissue growth in a human having a primary breast tumor (claims 205-221); (iii) reducing the blood supply to breast tumor tissue (claims 222-239); (iv) inhibiting angiogenesis in a breast carcinoma (claims 240-251); (v) inhibiting solid tumor growth in a human previously treated for a first solid tumor (claims 252-269); and (vi) prophylaxis against metastasis in a human previously treated for a solid tumor (claims 270-286) (breast cancer was elected as a species for all the claims). The

Examiner has alleged that the primary references, Cheresh and Kim, teach administration of $\alpha_v\beta_3$ /RGD-specific inhibitors, including the anti- $\alpha_v\beta_3$ antibody LM 609, to inhibit tumor cell attachment via vitronectin, fibrinogen and von Willebrand factor in vivo. The Examiner admits that the primary references do not disclose treatment of breast cancer or provide "angiogenesis-inhibiting amounts" (although the Examiner asserts that a "tumor-inhibiting amount" would intrinsically or expectedly encompass the "angiogenesis-inhibiting amount" recited by the claims). The Examiner further alleges that Pignatelli teaches that $\alpha_v\beta_3$ is expressed on breast tumor cells and that overexpression of integrins may contribute to metastasis and that Nip suggests $\alpha_v\beta_3$ -mediated interactions play a role in metastasis. Nicosia, according to the Examiner, teaches inhibiting angiogenesis with RGD inhibitors (which interact with $\alpha_v\beta_3$ among many other targets) and Folkman teaches that angiogenesis inhibitors can be used in conjunction with conventional therapy to control metastatic disease. Thus, the Examiner concludes that combining all of these references renders the claimed invention obvious.

The rejection of the claims is traversed for the reasons described below. In sum, the rejection should be withdrawn since (i) the cited references fail to suggest the claimed invention; (ii) the cited references fail to provide the legally required "reasonable expectation of success"; (iii) there would have been no motivation to combine the secondary references with the primary references and with each other; and (iv) even if combined, the secondary references cited by the Examiner actually teach away from the claimed invention.

To find obviousness, there must be a reason or suggestion in the art for carrying out the invention, other than the knowledge learned from the Applicants' disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). The proper inquiry is whether the art suggested the invention at the time the invention was made, and whether the art would have provided one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the

Applicants' disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Prior art references may be combined to render an alleged invention obvious under 35 U.S.C. § 103, but teachings of references can be combined only if there would have been some suggestion or incentive to do so. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1575 (Fed. Cir. 1984). The Federal Circuit has indicated that a *prima facie* case of obviousness requires "objective evidence of record" demonstrating that there is prior art that teaches or suggests combining the asserted references as proposed. *In re Lee*, 277 F.3d 1338, 1341 (Fed. Cir. 2002). The Court has also made clear that the requirement for a showing of the teaching or motivation to combine prior art references must be "clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence." *In re Dembiczaik*, 173 F.3d 994, 999 (Fed. Cir. 1999). Moreover, care must be exercised not to use the Applicant's disclosure to fill in the gaps in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985). Thus, Applicants' own teaching in the application in question also cannot constitute a proper basis for formulating obviousness rejections; hindsight reconstruction on the basis of an applicant's disclosure is impermissible. *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995); *In re Ochiai*, 71 F.3d 1565 (Fed. Cir. 1995).

The Primary References Fail to Suggest the Claimed Invention

The Examiner cites Kim and Cheresh as the primary references. At best, Kim and Cheresh teach that neutralizing antibodies that bind $\alpha_v\beta_3$ inhibit melanoma tumor growth and metastasis because tumor growth depends on cell attachment. Neither Kim nor Cheresh disclose or suggest the administration of antibodies immunospecific for $\alpha_v\beta_3$ for targeting the cancer of breast tissue or preventing metastasis. In fact, Kim and Cheresh both teach that antibodies against $\alpha_v\beta_3$ only react with certain types of tumor cells and react weakly if at all with other tumor cell types (Kim at page 13 (Table 2) and Cheresh at Figure 7). Kim does not provide any *in vivo* results and Cheresh provides one example

in which LM609 was administered intraperitoneally to mice having human melanoma tumor grafts and reportedly slowed tumor graft growth as compared to controls (Cheresh at pages 47-48).

Kim and Cheresh both fail to recognize that antibodies immunospecific for $\alpha_v\beta_3$ can be used in inhibiting angiogenesis. Although Kim and Cheresh suggest the utility of antibodies immunospecific for $\alpha_v\beta_3$ against cancer cells expressing $\alpha_v\beta_3$ as exemplified by *in vivo* results in melanoma, Kim and Cheresh do not disclose or suggest the use of antibodies immunospecific for $\alpha_v\beta_3$ in targeting other cancer cell-types that may or may not express $\alpha_v\beta_3$ by inhibition of angiogenesis, e.g., targeting breast tissue cancer. Kim explicitly teaches that anti- $\alpha_v\beta_3$ antibodies could not be used to treat tumor cells that do not bind the antibody (Kim at page 9, lines 12-14). In addition, although Kim suggests the administration of antibody in combination with other agents could be effective for the same clinical objective, neither Kim nor Cheresh disclose or suggest using antibodies immunospecific for $\alpha_v\beta_3$ for treating specific types of patients, e.g., those previously treated for a tumor.

In addition, Applicants disagree with the Examiner that tumor-inhibiting amounts of an antibody immunospecific for $\alpha_v\beta_3$ as taught by Cheresh, Kim, or Nip encompass "angiogenesis-inhibiting amounts". Only Cheresh actually disclosed tumor inhibition *in vivo* by an amount of an $\alpha_v\beta_3$ antibody, and, in Cheresh, those amounts were administered to mice having grafted human melanoma tumors. There is no evidence in the references that this tumor-inhibiting amount in mouse melanoma models in any way encompasses an angiogenesis-inhibiting amount. Moreover, tumor-inhibiting amounts alleged/proposed in the art for a particular type of tumor and/or patient (e.g., human patients having melanoma) have no correlation whatsoever to the angiogenesis-inhibiting amount for different type of tumor in a different patient or vice versa. Methods encompassing administering the tumor-inhibiting amounts to one type of tumor cell and/or patient are wholly irrelevant and suggest nothing about angiogenesis-inhibiting amounts administered to a different type of tumor cell and/or patient. Thus, there is no

evidence that the prior art disclosures suggest, much less disclose, inherently encompass angiogenesis inhibiting amounts.

More importantly, the law requires more than a mere suggestion. The suggestion, which is not present in the instant case must provide the skilled artisan with a reasonable expectation of success in achieving the claimed invention. The disclosures of Kim and Cheresh are far from providing such a heightened expectation. Further, when the art as a whole is considered, it is clear that no such reasonable expectation of success can survive the arts' teaching away.

In sum, the disclosures of the primary references do not suggest the claimed invention, much less, suggest that one of ordinary skill in the art could have practiced the claimed invention with any reasonable expectation of success.

The Secondary References Do Not Cure the Defects of the Primary References and
Actually Teach Away From the Claimed Invention

The Examiner has cited secondary references which do not cure the defects of the primary references, but in fact, on balance, teach away from the claimed invention.

Pignatelli

Pignatelli reports the results of an immunohistochemical study on the levels of various integrins in a series of invasive breast carcinomas. The experimental results reported in Pignatelli not only fail to cure the deficiencies of the cited primary references, but also teach away from the use of a $\alpha_v\beta_3$ as a target for treatment of breast cancer. Specifically, Pignatelli teaches away from targeting $\alpha_v\beta_3$ for inhibition or prevention of breast carcinoma progression. The data provided in Pignatelli Tables 2 and 3 (at pages 1163 and 1164) demonstrate that $\alpha_v\beta_3$ is only weakly expressed in 50% of the invasive lobular carcinomas characterized (see Table 2 at page 1163) and only weakly expressed in one of the nineteen invasive ductal carcinomas characterized (see Table 3 at page 1164). In contrast, $\alpha\beta$ complexes other than $\alpha_v\beta_3$ were more highly expressed in the

carcinomas.

Based upon the teachings of Pignatelli, the overexpression or lack thereof of certain integrins, including $\alpha_v\beta_3$, is indicative of a role in the progression of an invasive carcinoma (Pignatelli at page 1164). Therefore, the non-existent or weak expression of $\alpha_v\beta_3$, in comparison to other integrins, in carcinomas as reported by Pignatelli suggests to one skilled in the art that $\alpha_v\beta_3$ would not play a significant role in the progression of invasive breast carcinomas as would other more highly expressed integrins. Accordingly, it would have been highly unlikely that one of ordinary skill in the art would have targeted $\alpha_v\beta_3$ for treatment of invasive carcinomas, such as breast carcinoma based upon Pignatelli. Following the teachings of Pignatelli, one skilled in the art would have been more apt to target $\alpha\beta$ complexes other than $\alpha_v\beta_3$ for breast cancer therapy. At best, according to Pignatelli, overexpression of integrin molecules mediating cell migration may allow tumor cells to invade adjacent channels and contribute to metastasis and that the detection of α_v chain (and not necessarily $\alpha_v\beta_3$) in poorly differentiated carcinomas is suggestive of a similar role of vitronectin receptor in the progression of invasive breast carcinomas.

Not only does Pignatelli teach away from use of anti- $\alpha_v\beta_3$ antibodies in the treatment of cancer, Pignatelli does not teach or suggest *any* anti-integrin antibodies. Moreover, Pignatelli fails to suggest that angiogenesis might contribute to cancer progression. Thus, Pignatelli specifically teaches away from targeting $\alpha_v\beta_3$ for breast cancer therapy. Pignatelli does not cure the deficiencies of the cited primary references and, in fact, highlights the non-obviousness of the claimed invention.

Nip

Nip, like Cheresh and Kim, reports on *in vitro* studies exploring activity of an antibody immunospecific for $\alpha_v\beta_3$ for targeting melanoma. Nip reports that an antibody immunospecific for $\alpha_v\beta_3$ appears to block the adhesion of melanoma cells to cryostat sections of lymph node tissue *in vitro*. However, Nip reports that the incidence and

growth rate of primary tumors were unaffected by treatment with anti- $\alpha_v\beta_3$ antibodies (see Nip, page 1408, left col.). As such, Nip certainly teaches away from the use of an antibody immunospecific for $\alpha_v\beta_3$ to inhibit solid tumor growth in a human previously treated for a first solid tumor as recited in claims 172 and 173 and 252 to 269. In other words, Nip not only fails to remedy the deficiencies of the primary references, but Nip also teaches away from the use of antibodies immunospecific for $\alpha_v\beta_3$ in the treatment of solid tumors.

At best, Nip suggests that because $\alpha_v\beta_3$ appears to play a role in the increased metastatic potential of melanoma tumor cells, $\alpha_v\beta_3$ antibodies should be tried for targeting malignant melanoma during the early stages of dissemination. However, as the Examiner is aware, obvious to try is not the proper legal standard. Nip also fails to disclose or suggest that such $\alpha_v\beta_3$ antibodies could be used to treat cancer other than melanoma, such as cancer of breast tissue (which Pignatelli suggests they could not). Moreover, Nip, like Kim and Cheresh, fails to recognize the use of such an antibody as an angiogenesis inhibitor or the role of angiogenesis in tumor growth or metastasis.

In sum, even in combination with all the other references, Nip fails to disclose or suggest the claimed invention, provide the legally requisite reasonable expectation of success, and, indeed, teaches away from the use of an antibody immunospecific for $\alpha_v\beta_3$ to inhibit solid tumor growth.

Nicosia

Nicosia is cited by the Examiner for teaching inhibiting angiogenesis by an RGD inhibitor. According to Nicosia, RGD-containing peptides (which compete with RGD-containing ECM molecules for binding to integrins) inhibit angiogenesis *in vitro*. Nicosia does not teach or even suggest that antibodies immunospecific for $\alpha_v\beta_3$ could be used to inhibit angiogenesis. At best, Nicosia teaches that many receptors of the integrin family bind RGD sequences and, thus, are targets for RGD-containing peptide action. Nicosia does not mention specifically that $\alpha_v\beta_3$ is a target for inhibiting angiogenesis and, thus, in

view of Nicosia, the ordinarily skilled artisan would not have chosen $\alpha_v\beta_3$ for anti-angiogenic therapy. Furthermore, Nicosia does not teach the administration of the RGD inhibitor to target breast cancer cells, nor does Nicosia teach or suggest the use of such an RGD inhibitor for preventing or inhibiting solid tumor growth or metastasis. Nicosia certainly does not teach or even suggest that the RGD-containing peptides could be administered to a patient population previously treated for a first solid tumor. Even assuming, *arguendo*, that Nicosia did suggest that it was "obvious to try" an RGD-peptide for $\alpha_v\beta_3$ associated disease, this suggests nothing about $\alpha_v\beta_3$ antibodies, much less provide the requisite reasonable expectation of success. In sum, Nicosia fails to suggest the claimed invention and cannot cure the deficiencies of the primary references.

Folkman

Folkman reviews the use of angiogenesis as possible anti-cancer therapy as of 1992. Folkman does not cure the deficiencies of Cheresh and Kim because Folkman does not teach that $\alpha_v\beta_3$ antibodies are anti-angiogenic and provides no expectation of success. The Examiner alleges that Folkman teaches that angiogenesis inhibitors may be administered to cancer patients in conjunction with conventional chemotherapy for the control of metastatic disease. That may be the case. However, neither Folkman, nor any of the other cited references for that matter, teach that antibodies against $\alpha_v\beta_3$ can inhibit angiogenesis. Without that teaching or suggestion that $\alpha_v\beta_3$ antibodies could be anti-angiogenic, Folkman simply cannot suggest using $\alpha_v\beta_3$ antibodies as angiogenesis inhibitors for cancer therapy.

Even assuming, just for argument's sake, that the potential anti-angiogenic properties of $\alpha_v\beta_3$ antibodies had been suggested in the art, Folkman fails to provide the requisite expectation of success to support a legally sufficient case of obviousness. Folkman suggests that the absence of angiogenesis can severely restrict tumor growth and that angiogenesis inhibitors may have a use in cancer therapy in conjunction with conventional chemotherapy treatments. Folkman cautions that there are no general

principles for discovering angiogenesis inhibitors (see Folkman at page 89, right col.), and molecules that have anti-angiogenic activity in an animal model do not necessarily have anti-tumor effects even in mice and, furthermore, may be poor therapeutics due to high toxicity or poor bioavailability (Folkman at page 91). The take-home message from Folkman is that there would be a limited possibility of success in using a particular angiogenesis inhibitor as a cancer therapeutic. For these reasons, Folkman, even when combined with the other secondary references, does not cure the deficiencies of the primary references, and, in fact, weakens a contention that the primary references provide a suggestion and reasonable expectation of success.

Not Only Do the Primary and Secondary References Fail to Suggest Claimed Invention Obvious, But There Is Also No Motivation For the Asserted Combination of Primary and Secondary References

Moreover, in rejecting the instant claims, the Examiner has cited the above combination of six references yet has not demonstrated a prior art motivation for the asserted combination of these references. The Examiner does not provide any evidence, as required by the law, of motivation to combine the primary references Kim or Cheresh with any of the cited secondary references, much less all of them, to make the invention obvious. *In re Lee*, 277 F3d 1338, 1341 (Fed. Cir. 2002). The Examiner makes conclusory statements regarding the teachings of each of the secondary references but does not demonstrate the teaching or suggestion in the cited references that provides the motivation to combine. One skilled in the art would not have been motivated to combine all of these cited references at the time of the invention without a teaching or suggestion in the references or prior art to do so. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Moreover, as described *infra* with respect to the subject matter of the instant claims, not only would one skilled in the art have been unmotivated to combine the cited references, but one skilled in the art would also have had no reasonable expectation that the asserted combination of references would be successful in obtaining

and practicing the claimed invention.

In particular, there would have been no motivation to combine Pignatelli with the primary references Kim and Cheresh, because, as discussed above, Pignatelli teaches away from targeting $\alpha_v\beta_3$ in breast cancer therapy. There likewise would have been no motivation to combine the references that teach that $\alpha_v\beta_3$ antibodies and other $\alpha_v\beta_3$ -specific inhibitors may inhibit tumor, particularly melanoma tumor growth, and metastasis, *i.e.*, Kim, Cheresh, and Nip, with either of the secondary references Nicosia or Folkman. Nicosia teaches that a number of cell surface molecules, including integrins as a group and fibronectin, laminin, collagen, thrombospondin and fibrinogen, all have RGD sequences and may be involved in the attachment and migration of endothelial cells during angiogenesis. An RGD peptide, which could interact with any number of these molecules, inhibits angiogenesis *in vitro*. Nicosia does not mention $\alpha_v\beta_3$ or even speculate which of the RGD containing proteins could be specific targets for anti-angiogenesis. In light of Nicosia, one would have had no reason to consider $\alpha_v\beta_3$ as a target to inhibit angiogenesis. Thus, there is no nexus between Kim, Cheresh and Nicosia. And, without the link between $\alpha_v\beta_3$ and angiogenesis, there would have been absolutely no motivation to combine any of the references with Folkman, which discusses the use of angiogenesis inhibitors in cancer therapy, but does not mention or suggest $\alpha_v\beta_3$ as a target for inhibiting angiogenesis. In sum, the cited references do not make a *prima facie* case of obviousness because there would have been no motivation to combine the references at the time the invention was made.

The Examiner Improperly Ignores Claim Elements

The Examiner also indicates that certain claimed limitations, *e.g.*, specific dosages or modes of administration such as peristaltic administration and following surgery to remove a solid tumor, are not taught in the references yet were conventional at the time the invention was made. Such conclusory statements are insufficient to support a rejection. More significantly, since no angiogenesis treatment was known at the time of the invention, these contentions are factually incorrect. (See Folkman.) Because, for all

the reasons discussed above, the independent claims are patentable, the dependent claims which specify certain dosages, modes of administration and regimens are also patentable and have additional, perhaps independent, basis, for patentability.

In sum, Applicants submit that the references cited by the Examiner would not make the claimed invention obvious. Accordingly, Applicants believe claims 171-188 and 205-286 to be patentable and request the Examiner to reconsider and withdraw the instant rejection.

Summary

Applicants believe that a complete response is provided in the foregoing remarks to each issue and grounds for rejection and objection raised by the Examiner. Applicants submit that patentable subject matter exists with regard to the pending claims and therefore respectfully requests favorable action and entry of the present Response. The application is now believed to be in proper condition for allowance and early notification of allowance is earnestly solicited. The Examiner is invited to telephone the undersigned if it would be deemed helpful to advance the application.

Respectfully submitted,

11/27/02

Date

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